The electrocardiogram characteristics and pacing parameters of Permanent left bundle branch area pacing : A systematic review and meta-analysis

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Abstract

Background : The invention of His bundle pacing technology bring a new revelation–Left bundle branch area pacing (LBBAP). LBBAP engages in the electrical activation through left bundle branch area and produces ventricular electrical synchronization, which can grab more cardiac cells and increase the safety of pacing compared to His bundle pacing (HBP). This pacing has been considered as an attractive mode to achieve normal physiological pace markers. However,as a new technology, LBBAP is still in the stage of clinical exploration and lacks adequate evaluation. Objective :This study aims to investigate the electrocardiogram characteristics,pacing parameters,the safety and the effectiveness of LBBAP. Method : A computerized search of PubMed, Embase, The CochraneLibrary, Chinese CNKI, CBM, Wanfang and Weipu Chinese Sci-tech Journals database for effects of Left bundle pacing. The baseline characteristics, the successful rate of implantation, capture threshold, R-wave amplitude, pacing impedance, QRS duration and follow-up date were extracted and summarized. Results : Thirteen studies including 618 patients were included in this analysis. The overall successful rate for implantation was 92.1%.Permanent LBBAP resulted in narrow QRS duration when patients with QRS duration¿120ms after implantation (P=0.02). QRS duration and capture threshold of LBBAP remained stable during follow-up. Moreover, there was a trend of increased R-wave amplitude and declined pacing impedance at follow-up compared to implantation (P=0.003 and P¡0.00001, respectively). Conclusion : Permanent LBBAP has shown promising results in pacemaker-indicated patients. Good electrical synchronization, high success rates, and stable pacemaker parameters point to the unparalleled advantages of LBBAP in physiological pacing.

1.INTRODUCTION

cardiac pacing technology as a therapy has been used for over a half century and it remains the most effective therapy for bradycardia and cardiac conduction dysfunction.Traditionally, the pacing site at the apex of the right ventricle has been chosen because of the ease of placement of transvenous pacing leads. Several studies conducted over the past two decades have shown that right ventricular pacing (RVP)has adverse effects on clinical outcomes because of ventricular mechanical asynchrony which is secondary to electrical asynchrony[1–3]. The Pursuit of alternate pacing sites has been widely studied but no definitive conclusion is reached[4]. In 2000, Deshmukh conducted the pioneering investigation of permanent direct His bundle pacing(HBP)[5].Since then, more and more studies showed that HBP is superior in preserving electrical synchrony and left ventricular(LV)function compared to right ventricular pacing (RVP)[6,7]. However, lead placement for HBP is a technically challenging due to its anatomic location, and long-term capture thresholds of HBP have been found to be significantly higher than those of RVP. In 2017, Huang Weijian proposed left bundle branch area pacing (LBBAP) firstly[8]. Some clinical trials have demonstrated that left bundle branch area pacing exhibited the feasibility for patient with left bundle branch block (LBBB)/heart failure and showed more stable and reliable pacing parameters,but these trials mostly were small sample,short-term

studies. LBBAP may be a potential physiological pacing method that can replaces HBP, but it lacks of clinical application and requires to investigate the electrocardiogram characteristics, pacing parameters ,the safety and the effectiveness .

So we systematically reviewed currently available literature and carried out this meta-analysis: (i) to investigate the electrocardiogram characteristics change (ii)to report the stability of pacing parameters and (iii)to summuerize the successful rate of LBBAP from kinds of articles. The reporting of this systematic review follows current standards.

2.METHODS

2.1 Data sources and searches

We conducted a systematic search of electronic databases including PubMed, Embase and etc. The search was limited to full-text English or Chinese publications before 31 December 2019. The search terms included "Left bundle branch area " or "LBBAP" and "pacing".

2.2 Study selection and data abstraction

The abstracts retrieved from the search were reviewed by two investigators. Articles were included :(1) Study type:observational study and randomized controlled study; (2)study object: patients who need permanent pacemaker implantation; (3)clearly define the conditions for LBBAP success; (4)The ECG characteristics and pacing parameters of baseline and follow-up including QRS duration, capture threshold, R-wave amplitude (perception), impedance, etc. (5)have a clear follow-up time. Articles were excluded: (1) report the acute response only and follow-up time of LBBAP less than 1 month; (2)repeated data from the same research center, unable to obtain full text or original data after contacting the author; (3)case reports, animal studies etc.; (4)documents in languages other than Chinese and English. The extracted data included gender, age, indication of device implantation, number of enrolled patients, success rate of implantation, follow-up time, QRS duration at baseline and follow-up, capture threshold at baseline and follow-up, R-wave amplitude at baseline and follow-up, impedance at baseline and follow-up. For continuous variables, means, standard deviations, and sample sizes were extracted to estimate the overall average values.

2.3 Statistical analysis

Review Manager 5.3 (Cochrane, London, UK) was used to perform data analysis using random effects models. Statistical heterogeneity was assessed using the I^2 statistic. Sensitivity analyses were conducted to identify potential heterogeneity by leaving out any study. Publication bias was evaluated by generating a funnel plot of the logarithm of effect size against the standard error for each trial.

P ¡ 0.05 was considered statistically significant in all analyses.

3.RESULTS

3.1 Study characteristics

Figure 1 shows the results of the search and selection process. Thirteen studies including 618 patients were included in these meta-analyses. The average age of the patients was 69.4 years and 299 of patients were male(48.3%). The overall successful rate of LBBAP was 92% (569/618). (Table1)

3.2.1 QRS duration at baseline and implantation

For patients with QRS duration<120ms, no significant difference was observed between baseline and paced QRS duration (107.3± 24.8ms vs 115.3 ±10.9 ms, P = 0.28 I^2 = 92%,Figure 2A). For patients with QRS duration>120ms, the paced QRS duration was markedly decreased from 140.2 +- 34.2ms at baseline to 133.1 +- 16.7ms after LBBAP (P =0.02, I^2 = 92%, Figure 2B), representing a mean narrowing of QRS duration.

3.2.2 QRS duration after implantation and follow-up

Despite there are various follow-up time,we adopt the longest follow-up time of every article that we can achieve and all follow-up time >1 month at least. Patients accepted LBBAP have stable QRS duration when it compared to implantation (P =0.19, $I^2 = 0\%$, Figure 3).

3.3 Capture threshold at baseline and follow-up

Despite the difference in follow-up time, our study did not show the same situation as HBP[6], the capture threshold did not increase with longer follow-up time, and there was no statistically significant difference between the postoperative capture threshold and the follow-up threshold (P =0.95, $I^2 = 91\%$, Figure 4).

3.4R-waveamplitude at baseline and follow-up

After aggregating all studies that recorded R-wave amplitude with relevant follow-up data, we found a significant trend of elevated R-wave amplitude which was statistically significant when comparing the data collected after surgery and at follow-up(12.17+-5.24mv VS 14.22+-5.47mv ,P =0.003, $I^2 = 50\%$, Figure 5).

3.5 Impedance at baseline and follow-up

The data revealed a clear trend of decreasing pacing impedance at follow-up and a statistically significant correlation between the postoperative and the follow-up, which may be related to the remission of edema and the formation of fibrous scarring at the electrode fixation site. (684.51+-134.15Ω vs 532.15±104.24Ω P¡0.00001, $I^2 =85\%$, Figure 6)

3.6 LBBAP success rate and associated complications

In the included studies, the highest success rate was 100%, the lowest success rate was 66.7%, and the average success rate was 92%.

It should be noted in particular that the study conducted by author Chen Lu was a discussion of the success rate, safety and efficacy of LBBAP surgery.Their retrospective case study was divided into two distinct phases, namely, the learning phase and the proficient surgery phase,and there was a significant difference in the success rates of the two phases, which were 55.6% and 88.9, respectively, with a mean success rate of 66.7%.

In terms of surgery-related complications, one patient in Xiaofei Li's study developed a ventricular septal perforation shortly after surgery and successfully repaired it; In Pugazhendhi Vijayaraman's study, three patients presented with acute lead dislodgments within 24 hours after surgery, and these three patients subsequently underwent surgery and were successfully repaired. In the third patient, another ventricular septal perforation occurred during the re-repair procedure, and the electrode was re-fixed slightly below the previous fixation point. One patient developed a pericardial effusion as a result of uninterrupted oral anticoagulation, which disappeared after puncture drainage; In Yuqiu Li's study, one patient who was receiving dual antiplatelet therapy developed a pockethematoma; In Jingfeng Wang's study, one patient suffered an intraoperative septal lead perforation and three patients developed mild pocket hematoma within one month of surgery, and all hematoma was relieved by reinforced elastic bandage compression. Two patients experienced lead dislodgement. One was noted 2 months post-implant, who received LBBAP again; while another occurred 4 months post-implant with the lead relocated to RVS.

3.7 Sensitivity analysis

Sensitivity analysis by leaving out any study did not influence the direction or magnitude of the above results, indicating that no single study overly affected most of the findings. Due to the limited number of included studies for correction threshold, sensitivity analysis might not be suitable in the situation. Funnel plot of the included studies showed that no obvious publication bias was found(Figure 7).

4 DISCUSSION

The value of this meta-analysis on LBBAP is that it included almost all types of patients with pacing indications, and self control study showed that LBBAP had a good therapeutic effect. Our meta-analysis

demonstrated that: (1) LBBAP produces a favorable QRS duration, not only stabilizing patients with a normal QRS duration, but also significantly shortening the prolonged QRS duration; (2)In patients receiving LBBAP, there are the following changes in pacemaker parameters after a period of follow-up: a. the stable capture threshold for a long time; b.a positive trend in R-wave amplitude; c. a negative trend in pacing impedance; (3) In the included studies, the average success rate of LBBAP was high, the overall safety of the procedure was reliable, and there were no specific complications of pacemaker surgery.

It has been confirmed that RV apical pacing was associated with high incidence of heart failure, AF, and mortality due to its abnormal activation propagation and obvious LV contraction delay[23-24].Other pacing sites just like the septum or outflow tract did not show obvious results in improving clinical outcomes[25-26].Up to now, His-bundle pacing was considered as the physiological pacing method. However, challenges with His bundle pacing including difficulty in identifying the location of the His bundle, a relative high capture threshold with potential long-term instability, especially in patients who already have cardiac conduction disease such as LBBB, which withheld the widespread application of this pacing[6,27].

. Pacing the LBB that directly capture the left bundle branch by deep septal pacing was first introduced by Huang in 2017[8], which is likely to fill many of the deficits of HBP.The left bundle branch is flat banded and fan-shaped in the subendocardium, with a wider distribution than His bundle and fewer fiber wrapping[28,29]. For the LBBAP procedure, the anatomic characteristics of the LBB provide a relatively large area for the selection of a pacing site. Lead fixation could be more easily achieved by screwing the lead into the ventricular septum. Baseline bundle branch block might be more likely corrected by LBBAP beyond the site of block[8,17].

The sequence of ventricular excitation and ventricular systolic synchrony are two important factors affecting postoperative cardiac function. The coherence and similarity of the QRS morphology between intrinsic QRS and paced QRS can indirectly reflect the difference of the sequence of downward transmission and ventricular excitation. So the QRS duration is an important indicator of the synchronization of the contractions of both ventricles, which affects the risk of death and heart failure in patients after pacing surgery[30-32]. LBBAP proved its effectiveness both in maintaining a normal QRS duration and in generating narrower QRS duration in our study. The rich myocardial tissue surrounding the electrodes guarantee the characteristic of higher R-wave amplitude with a lower threshold for LBBAP, which was also confirmed in our study. These stable pacing parameters indicated that some sensing or threshold issues that are common in HBP or RVP might be avoided in LBBAP.

In our included study, LBBAP was shown to be effective in the treatment of slow arrhythmias such as AVB and SND. In particular, in patients with HBP failure or CRT indications, LBBAP can maintain better electrical and mechanical synchronization, and its efficacy and safety have been further validated as an excellent alternative to HBP.So it could become a mainstream pacing technology in the future.

5.STUDY LIMITATION

There are several limitations of this meta-analysis. First, the number of included patients was limited and most of the studies were cohort studies with inherent limitations that reduced the internal validity compared to randomized controlled trials. Second, there are limited data on the effect size of LBBAP on outcomes as the studies included were observational and did not all have comparative arms. Next, some data, including pacing pulse width and follow-up time, were variable and inconsistent, which may influence the study uniformity. In addition, there was no uniformity at this time in measuring QRS durations with selective and nonselective LBBAP. Finally, the indications for pacemaker placement defined by the studies we included were not uniform and were broad in scope. On the one hand, this demonstrates the great potential and promise of LBBAP for apply in patients with all types of pacemaker indications, and on the other hand, it creates an inevitable heterogeneity in the statistical analysis we perform.

6.CONCLUSIONS

Over a certain follow-up time, LBBAP has stable pacing parameters and these indicate a good clinical prognosis. Meanwhile Long-term safety and capture threshold should be continually monitored and awaited

from further observation. Randomized controlled trials are needed to assess the efficacy of LBBAP.

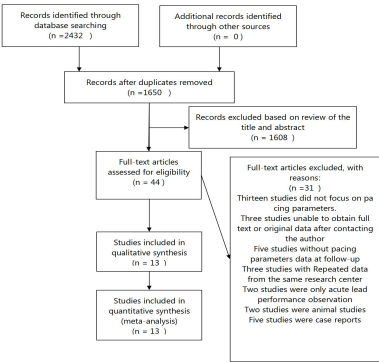## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING

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Records identified through database searching
(n =2432)

Additional records identified through other sources
(n = 0)

Records after duplicates removed
(n =1650)

Records excluded based on review of the title and abstract
(n = 1608)

Full-text articles assessed for eligibility
(n = 44)

Full-text articles excluded, with reasons:
(n =31)
Thirteen studies did not focus on pacing parameters.
Three studies unable to obtain full text or original data after contacting the author
Five studies without pacing parameters data at follow-up
Three studies with Repeated data from the same research center
Two studies were only acute lead performance observation
Two studies were animal studies
Five studies were case reports

Studies included in qualitative synthesis
(n = 13)

Studies included in quantitative synthesis (meta-analysis)
(n = 13)

(**Figure 1** Flowchart of selection process for articles included in the meta-analysis)

Authors	Year	Design	Indication	Patient numeber	successful LBBAP	Follow-up time	Implant success(%)
Xiaofeng Hou[9]	2019	prospective cohort study	SND(16) or AVB(21) or AF with slow ventricular rate(19)	59	56	1M,6M	96%
Keping Chen[10]	2018	prospective cohort study	SND(15) or AVB(1) or RBBB(2) or LBBB(1)	20	20	3M	100%
Eriko Hasumi[11]	2019	prospective cohort study	HBP failed	21	17	1W,3M,6M	81%
Weiwei Zhang[12]	2019	prospective cohort study	HF and LBBB	11	11	3M,6M,12M	100%
Xiaofei Li[13]	2019	retrospective cohort study	AVB	33	30	3M	90.9%
Pugazhendhi Vijayaraman[14]	2019	prospective cohort study	SND(23) or AVB(54) or CRT(11)or HBP failed(7) or AV node ablation (7)	100	93	3M	93%
Yuqiu Li[15]	2018	prospective cohort study	SND(59) or AVB(28)	87	70	3M	80.4%
Jingfeng Wang[16]	2019	prospective cohort study	SND(22) or AVB(36) or AF with slow ventricular rate(8)	66	61	1M,3M,6M	92%
Su Lan[17]	2019	prospective cohort study	AVB	139	139	1M,3M,6M,12M	100%
ZENG Chun-miao[18]	2019	prospective cohort study	AVB(24) or AF with slow ventricular rate(1)	25	25	1W,3M,6M	100%
Chen Lu[19]	2019	retrospective cohort study	SND or AVB or AF with slow ventricular rate	27	18	3M	66.7%
QIAN Zhihong[20]	2018	retrospective cohort study	AF with slow ventricular rate	10	10	7D,30D,3M,6M	100%
Ren Cheng[21]	2019	retrospective cohort study	SND(6) or AVB（9） or AF with slow ventricular rate（3）CRT failed(1) pacemaker reimplantation(1)	20	19	1W,3M	95%
SND=sinus node dysfunction; AVB=atrioventricular block; AF=atrial fibrillation; HBP=His bundle pacing; LBBB=; CRT=Cardiac resynchronization therapy; LBBB=left bundle branch block; HF=atrioventricular block; AV node=atrioventricular node							

Table 1 General description of the included studies

1